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# SECTION 1

## DISORDERS OF GROWTH, SEXUAL DEVELOPMENT, AND PUBERTY

### Short Stature

### CHAPTER 1

**Donna S Eng,  
Ram K Menon**

#### CASE 1

A 14-year-old boy was brought to his doctor because he has noticed that he is shorter than his friends. He is otherwise healthy and is active in sports. Growth charts sent from his pediatrician's office are noted in [Figure 1](#).

He was seen at his pediatrician's office 6 months ago and based on his last height measurement, his calculated growth velocity was 5.4 cm/year.

**Past medical history:** None.

**Family history:** Father's height is 177 cm and mother measures 170 cm. His father did not complete statural growth until he was 18–19 years of age.

**Physical examination:** Height 148 cm (2%). Body mass index (BMI) 50th percentile. He is noted to have no acne. His pubertal examination reveals a testicular volume of 4 cc with sparse pubic hair.

**Radiology:** Bone age is 11–12 years.

#### Q: DOES HE HAVE SHORT STATURE?

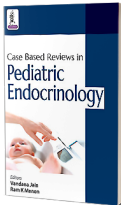
Short stature is defined as height below the third percentile or greater than two standard deviations (SDs) below the mean height for chronological age. The boy described above is at the second percentile for height and hence he does meet the criteria for short stature. Dwarfism refers to severe forms of short stature with height below three SD from the mean.

#### Q: WHAT ARE THE MOST IMPORTANT POINTS TO ELICIT IN HIS HISTORY AND PHYSICAL EXAMINATION?

#### HISTORY

A detailed history is the key to eliciting the etiology of short stature and should include the following elements:

- Prenatal history (maternal infection, consumption of alcohol, drugs)



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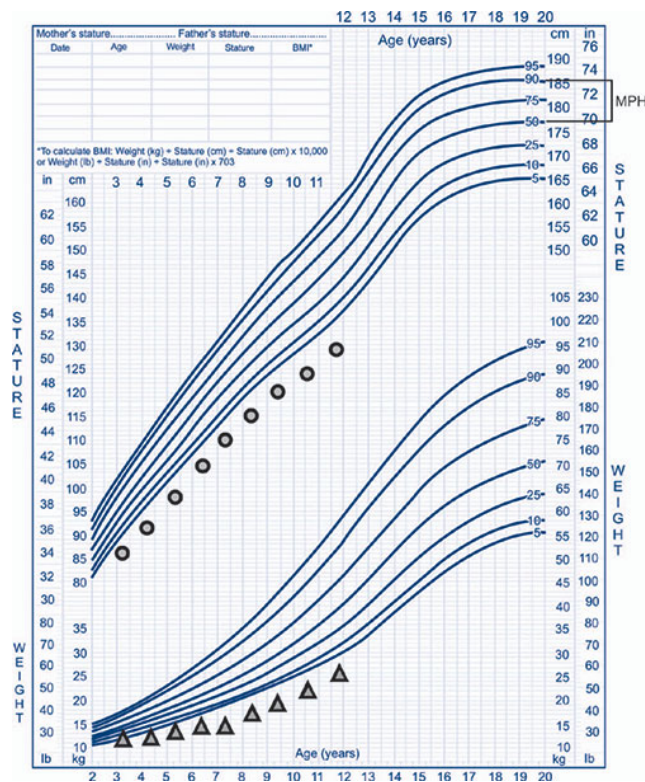


Figure 1: Growth chart (Case 1).

- Pattern of growth (height and weight) including birth weight and length in relation to gestational age
- Family history—parental heights, age of onset of puberty in parents and immediate relatives
- Profile of patient's pubertal development including onset of testicular and penile enlargement and pubic hair development
- Nutrition
- Evidence of systemic disease—gastrointestinal (GI), cardiac, pulmonary, renal
- Drug administration—glucocorticoids, methylphenidate
- Neurologic symptoms—especially headache, visual disturbance, recent history of enuresis
- Psychosocial milieu.

## PHYSICAL EXAMINATION

A comprehensive physical examination should be conducted with special emphasis on the following:

- Accurate measurements of height, weight, head circumference, arm span, upper and lower body segment ratio
- Abnormal pigmentation of the skin (e.g., café-au-lait pigmentation)
- Assess nutritional state and fat distribution
- Pubertal stage
- Dysmorphic features
- Examination of the thyroid gland
- Complete neurological exam including fundoscopy and visual fields.

## Q: HOW DO YOU INTERPRET HIS GROWTH VELOCITY AND ABSOLUTE HEIGHT?

Ascertainment of height velocity is the most important aspect of growth evaluation. Accurate determination requires a minimum of 6 months of observation. A normal height velocity for chronological age and pubertal stage is strong evidence against an endocrine (hormonal) cause for the short stature. Normal average growth rates for prepubertal children are 8 cm/year at 2 years, 7 cm/year at 3 years, and 5–6 cm/year from 4 years to 9 years of age. The boy described above has a growth velocity of 5.4 cm per year which is normal for a prepubertal child.

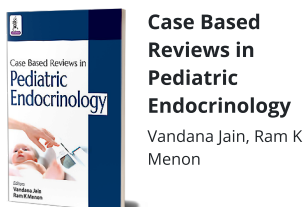
An impaired growth velocity is usually indicative of a pathological cause of short stature (Figure 2).

Absolute height should also be considered. An absolute height of three SDs below the mean is more likely to be pathologic than a height of one SD below the mean.

## Q: HOW DO YOU INTERPRET HIS BONE AGE?

Skeletal maturity assessment (bone age) is done by comparing the appearance of epiphyseal centers (left wrist) on radiography with age appropriate published standards.

The boy described above has a delayed bone age. The bone age itself is not diagnostic but can be used to aid in arriving at a diagnosis. A delayed bone age can be consistent with nonpathologic patterns of growth including constitutional delay of growth and development. However, delayed bone age can also be consistent with many pathologic causes of short stature including malnutrition, endocrine disorders [(e.g., growth hormone (GH) deficiency, hypothyroidism, Cushing's syndrome)], and chronic diseases (e.g., renal, cardiac, pulmonary, GI).



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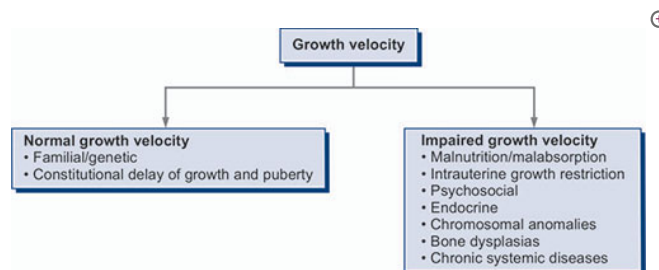


Figure 2: Impaired growth velocity (indicative of a pathological cause of short stature).

A bone age commensurate with chronological age can be associated with nonpathologic causes of short stature (familial/genetic short stature) or pathologic causes (dysgenetic/syndromic short stature, bone dysplasias).

A delayed bone age implies the presence of potential for growth. Hence normal or advanced bone age in a child with short stature is of greater concern than delayed bone age.

The main use of bone age is for predicting final adult height. Final adult height prediction from bone age can be made using nomograms. A commonly used nomogram is the Bayley-Pinneau nomogram. Using this nomogram, the predicted final height for this boy is 177 cm [bone age (BA) of 12 years] to 184 cm (BA of 11 years). This predicted height commensurates with the mid-parental height. A child's height is appropriate for the midparental height if the projected adult height is within  $\pm 8$  cm of the calculated midparental height.

### Q: WHAT IS THE MIDPARENTAL TARGET HEIGHT FOR THE CHILD DESCRIBED ABOVE?

Target height for males = [father's height (cm) + mother's height (cm) + 13]/2

Target height for females = [father's height (cm) + mother's height (cm) - 13]/2.

Thus, the midparental target height for the boy described above is (177 cm + 170 cm + 13 cm)/2 = 180 cm.

### Q: WHAT IS THE MOST LIKELY DIAGNOSIS?

An unremarkable history and physical examination, family history of delayed puberty, growth velocity normal for early Tanner 2 pubertal stage, and predicted final height commensurate with the midparental height is supportive of a diagnosis of constitutional delay of growth and puberty.

Constitutional delay of growth and puberty is characterized by delayed skeletal maturation and delayed onset of puberty. Final adult height and progression of sexual development are normal. Often there is a family history of delayed growth and onset of sexual development. Of note, growth velocity may be decreased in the first 2–3 years of life (catch down) but normal thereafter.

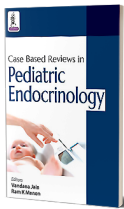
Familial or genetic short stature is also associated with normal growth velocity. In familial short stature final adult height is short but appropriate for midparental height. They may also have normal or relatively small weight and length at birth. In contrast to constitutional delay of growth, those with familial short stature will have normal onset and progression of puberty and bone age will be consistent with chronological age.

### Q: WHAT IS THE MOST APPROPRIATE NEXT STEP?

Observation over 6–9 months to establish a consistent pattern of growth velocity would be the most appropriate next step. If there is a slowing of the growth velocity during this observation period, further evaluation should be considered. When analyzing growth curves, it is important to keep in mind the reliability and accuracy of the measurements. Inaccurate plotting of measurements on the growth chart and measurement error are common reasons for misdiagnosis of growth disorders.

If there is significant psychosocial distress, a short course (3–6 months) of testosterone therapy may be considered to hasten the onset of puberty. The testosterone dose [50 mg of testosterone cypionate intramuscular every month] for this purpose is much less than a full replacement dose. It is not usually recommended prior to a bone age maturity of 12–13 years. In addition, constitutional delay of growth and

puberty is a diagnosis of exclusion, and testosterone treatment is recommended only after excluding organic pathology.



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## CASE 2

An 11-year-old girl from a rural area is seen for the first time in clinic.

Her mother reports she previously was growing at the 25th percentile for height but at today's visit she is below the fifth percentile. Growth chart is shown in [Figure 3](#).

**Past medical history:** She was previously healthy. Menarche was 1 year ago and menses have been irregular.

**Family history:** No significant family history.

**Social history:** She is doing well in school.

**Physical examination:** Height 130 cm (<5th percentile), weight is 32 kg (50th percentile), lower segment 67 cm. She has an overall stocky build. Tanner stage 2 breast development with no pubic hair was noted.

## Q: WHAT IS THE DIFFERENTIAL DIAGNOSIS FOR PATHOLOGIC CAUSES OF SHORT STATURE?

In considering the pathologic causes of short stature, it is useful to assess whether the short stature is proportionate or disproportionate. Disproportionate short stature is characterized by abnormal upper to lower body segment ratio for age. The lower segment is measured from symphysis pubis to the floor. The upper segment is equal to the height minus the lower segment. Mean upper segment to lower segment ratio is highest at birth and decreases into adulthood: 1.7 (birth), 1.3 (3 years), 1.0 (7 years), 0.9 (adult). Disproportionate causes of short stature include skeletal dysplasias (e.g., achondroplasia, hypochondroplasia), metabolic bone disease (e.g., rickets), and abnormalities of vertebral bodies. One should consider a bone survey for skeletal dysplasia if disproportionate short stature is suspected.

Proportionate short stature is characterized by normal upper to lower body segment ratio for age. In general, proportionate short stature is much more common than disproportionate short stature. The causes of proportionate short stature are varied. Endocrinopathies including GH deficiency/insensitivity, hypothyroidism, and Cushing's syndrome are usually associated with increased weight/height ratio. In contrast, malnutrition is typically accompanied by a decreased weight to height ratio. Malnutrition could be a result of GI pathology (malabsorption, inflammatory bowel disease, celiac disease), renal disease (renal tubular acidosis, chronic renal failure, nephrogenic diabetes insipidus), or other chronic disease, such as cardiac, pulmonary, liver, or chronic infection.

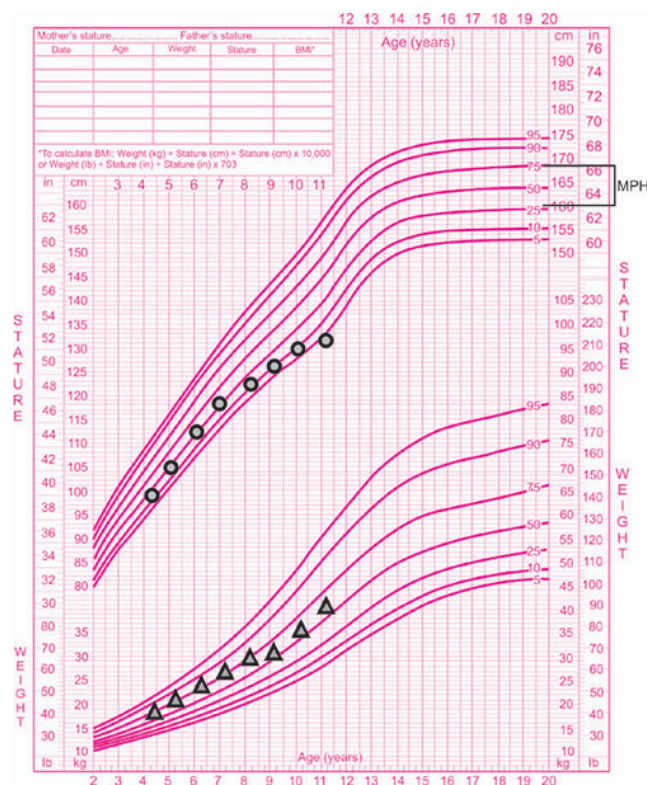


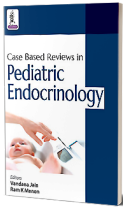
Figure 3: Growth chart (Case 2).

Intrauterine growth retardation (IUGR) is also associated with proportionate short stature. IUGR is defined as infants with birth weight less than two SDs from the mean for gestational age, sex, and race. Causes of IUGR include placental insufficiency, fetal infections, teratogens, and chromosomal abnormalities. If there are associated dysmorphic features, one may consider genetic conditions, such as trisomy 21 (Down's



syndrome), Prader-Willi syndrome, Russell-Silver syndrome (RSS), or Turner's syndrome. Of note, in Turner's syndrome, short stature is the most consistent and sometimes the only overt clinical sign.

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## Q: WHAT LABORATORY STUDIES WOULD YOU CONSIDER OBTAINING?

In review of this child's growth chart, it appears that she is a well-nourished child with deceleration in linear growth. Thus, endocrinopathies should be considered in this child and laboratory evaluation should include thyroid stimulating hormone (TSH) and free thyroxine (T4) where an elevated TSH and low free T4 indicates primary hypothyroidism; and insulin-like growth factor-1 (IGF1), somatomedin C] and insulin-like growth factor binding protein-3 (IGFBP3) where low levels are suggestive of GH deficiency. A peripheral blood karyotype should always be considered in a girl with short stature and especially if features suggest chromosomal abnormalities or a syndrome. Chronic diseases such as chronic renal failure, chronic liver disease, chronic anemia, or inflammatory bowel disease should be excluded by the appropriate screening tests.

## Q: HER TSH IS GREATER THAN 1000 MIU/L AND FREE T4 IS 0.2 NG/DL. WHAT ROLE DOES THYROID HORMONE PLAY IN GROWTH? IS HER EARLY MENARCHE RELATED TO HER DIAGNOSIS?

Thyroid hormone binds to the thyroid hormone-responsive element in the promoter of the GH gene and is essential for transcription of the GH gene. In addition to this direct effect on GH synthesis, thyroid hormone is required for the many cellular processes that play an essential role in normal growth. The clinical history suggests long-standing/severe primary hypothyroidism, which can cause growth arrest and precocious puberty (vanWyk-Grumbach syndrome). Girls may manifest breast development, galactorrhea, and precocious menstruation; however, development of pubic hair is usually delayed in these patients.

## Q: IF HER THYROID TESTS AND SCREENING TESTS FOR CHRONIC DISEASES (E.G., RENAL, LIVER) WERE NORMAL, WHAT DIAGNOSIS WOULD A LOW IGF1 AND IGFBP3 BE SUGGESTIVE OF?

Such a scenario would be suggestive of GH deficiency. If one is considering GH deficiency, the two questions that need to be addressed are (i) does the child have GH deficiency, and (ii) what is the etiology of the GH deficiency.

## Q: WHAT ARE THE CRITERIA TO MAKE A DIAGNOSIS OF GH DEFICIENCY (Box 1)?

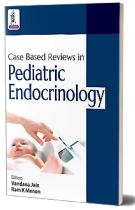
Growth hormone deficiency is a clinical diagnosis and not a laboratory diagnosis. The essential feature to make a diagnosis of GH deficiency is to document growth velocity that is low for age and pubertal status. A rule of thumb is that in a prepubertal child older than 3 years, a growth velocity of less than 4 cm/year is subnormal and deserves further investigation. A delayed bone age is also compatible with the diagnosis of GH deficiency. Since the secretion of GH from the pituitary gland is episodic in nature, measurement of random levels of GH in blood is of no value in the diagnosis of GH deficiency.

### Box 1 : Criteria For Diagnosing Growth Hormone (GH) Deficiency

- Clinical (*not* laboratory) diagnosis
- Growth velocity less than 2 SD for age and pubertal status
- Low IGF-1 and IGFBP-3
- Provocative ( $\times 2$  stimuli) GH level less than 7–10 ng/mL
- Corroborative evidence = delayed bone age

SD, standard derivation; IGF, insulin-like growth factor; IGFBP, insulin-like growth factor-binding protein; GH, growth hormone.

Traditionally the GH response to sequential administration of two provocative stimuli of GH secretion (e.g., insulin-induced hypoglycemia, arginine, clonidine, or glucagon) is used to test for GH deficiency. A peak concentration of GH more than 10 ng/mL is evidence against a diagnosis of GH deficiency a peak level between 5 ng/mL and 10 ng/mL is indeterminate, and a peak that is less than 5 ng/mL is supportive of GH deficiency. However, the precise cut-off levels need to be interpreted in conjunction with the characteristics (e.g., type of antibody used etc.) of the assay used to measure the GH concentration. It is important to remember that hypothyroidism can result in falsely low GH levels on the GH provocative tests and hence it is essential that the patient be euthyroid before the GH provocative tests are performed. The circulating levels of both IGF1 and IGFBP3 are dependent on GH. In contrast to GH, the circulatory levels of IGF1 and IGFBP3 are stable throughout the day and hence amenable to random measurement. IGF1 levels are also decreased in malnutrition and by itself a low IGF1 is not very useful in the diagnosis of GH. However, low levels of both IGF1 and IGFBP3 are suggestive of GH deficiency.



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## Q: WHAT ARE THE CAUSES OF GH DEFICIENCY?

The causes of GH deficiency will depend on the age [congenital (pituitary aplasia/pituitary hypoplasia/septicoptic dysplasia) vs. acquired], presence or deficiency of other pituitary hormone (isolated GH deficiency vs. pan hypopituitarism), and presence of other coexisting morbidities [(e.g., central nervous system (CNS) trauma, cranial irradiation). In many instances the etiology may remain undefined and these patients are classified as idiopathic GH deficiency.

## Q: HOW DO YOU TREAT GH DEFICIENCY?

Growth hormone deficiency is treated with daily subcutaneous injections of recombinant GH. The dose of GH in GH deficiency is 30–45 µg/kg per day × 7 days a week. The dose should be adjusted to attain appropriate increase in growth velocity. It is important to avoid features (acromegaloid) of GH excess. In this regard monitoring of IGF1 levels can be of use to make sure that the levels do not exceed the upper limit of normal for age and pubertal status.

## Q: WHAT ARE THE SIDE EFFECTS OF GH TREATMENT?

The side effects of GH treatment can be grouped into two categories:

### 1. Common but non-life threatening side-effects:

- Redness/swelling/pain at the injection site: To avoid this, rotate injection sites daily
- Decreased thyroid function (hypothyroidism): Patients treated with GH should have periodic thyroid function tests and appropriate thyroid replacement therapy should be initiated if necessary. Untreated hypothyroidism can prevent optimal response to GH treatment
- Fluid retention: Mostly seen in adults, and is transient and dose-dependent.

### 2. Special situations:

- Allergic reaction: Local reactions are more common and not life-threatening. Patients with known allergies to m-cresol should take caution. Preservative-free preparations are available
- Gynecomastia (enlargement of the breasts in boys): This is a rare side-effect of GH treatment. The enlargement is usually mild and subsides with time
- Diabetes mellitus: Patients with either type 1 diabetes or type 2 diabetes may require increased insulin doses to control elevated blood sugars which may occur with GH therapy
- Slipped capital femoral epiphyses (SCFE). Patients who are overweight/obese are at risk for developing SCFE. Any patient on GH therapy with new-onset or worsening hip pain/limp should be carefully evaluated
- Scoliosis: It can occur during periods of rapid growth. Preexisting scoliosis can be worsened with GH therapy, and therefore, careful monitoring is necessary. GH therapy may need to be discontinued depending on extent of progression
- Heart disease: Any patient with structural/functional heart disease must be closely followed by a cardiologist who must clear the patient for GH therapy Turner's syndrome is such a condition in which patients must be screened for heart disease prior to initiating GH treatment
- Active malignancy/cancer: GH therapy is discontinued in presence of active or recurrent malignancy. Any preexisting malignancy should be inactive and its treatment completed prior to instituting GH therapy. GH therapy does not cause cancer. However, some studies suggest that in patients with preexisting cancer, GH can increase the risk of a second cancer.

Intracranial hypertension: Reported in small number of patients treated with GH. Symptoms include severe/worsening headache, double/blurred vision (papilledema), nausea/vomiting, and/or change in mental status which represents increased pressure in the brain. Patients should seek medical attention right away to diagnose and treat this condition. This condition is abated by discontinuing GH therapy. This is a rare occurrence and usually avoided by starting GH therapy at the lowest effective dose and increasing it gradually based on patient's tolerance.

### CASE 3

A 13-year-old boy comes to clinic with complaints of fatigue and not growing. The growth chart from his pediatrician indicates that his weight was at the 50th percentile until 5 years ago when it was recorded at the 10th percentile and now is below the third percentile. Height was at the 50th percentile until 2 years ago when it was recorded at the 25th percentile. Today it is at the fifth percentile. Growth chart is noted in [Figure 4](#).

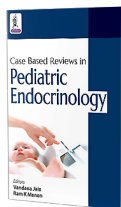
**Past medical history:** None.

**Family history:** None.

**Social history:** He is doing well in school.

**Physical examination:** Height 140 cm (5th percentile), weight is 30 kg (third percentile). BMI third percentile. Pubertal examination is notable for 8 cc testicles and Tanner stage 2 pubic hair.

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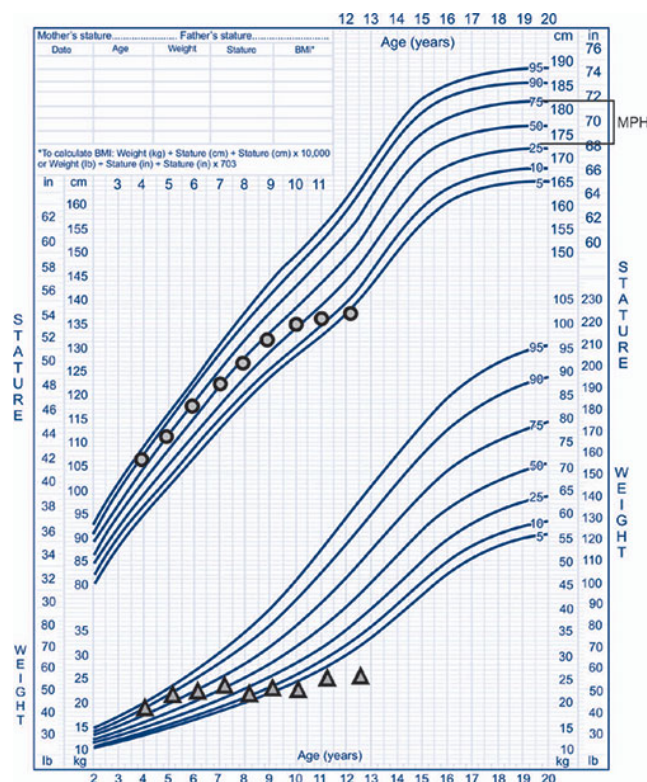


Figure 4: Growth chart (Case 3).

### Q: HOW DO YOU INTERPRET HIS GROWTH CHART (Figure 4)?

The child described in case 3 demonstrated slowed/no weight gain prior to his slowed height gain; thus, malnutrition should be considered as a cause of his short stature.

### Q: WHAT LABORATORY STUDIES DO YOU WANT TO INCLUDE IN YOUR EVALUATION?

Again, because a thin child with deceleration of linear growth suggests malnutrition, laboratory evaluation should be tailored to evaluate for systemic disorders that could result in malnutrition. A complete blood count (CBC) and sedimentation rate is helpful in identifying patients with inflammatory bowel disease or a chronic inflammatory process. Also consider including a celiac screen [e.g., endomysial immunoglobulin A (IgA) antibody and/or transglutaminase IgA antibody]. Note, the patient must have adequate IgA levels for this test to be valid. A urinalysis, serum creatinine, electrolytes, and hepatic function panel will evaluate for renal and liver disorders. If cystic fibrosis is suspected a sweat chloride test may also be indicated.

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### CASE 4

A 13-year-old boy presents with slowed growth. His mother is concerned because he has grown very little over the last few years. His growth chart is displayed Figure 5.

#### Past medical history:

**Asthma:** He has been diagnosed with moderate-severe asthma. His asthma has worsened over the last 2 years with multiple upper respiratory infections. His treatment for asthma has required several courses of oral glucocorticosteroids as well as increasing doses of daily inhaled glucocorticosteroids.

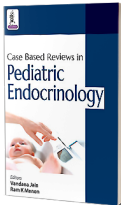
**Medications:** His current dose of daily inhaled corticosteroid is fluticasone propionate/salmeterol (250/50 µg) two puffs twice a day.

**Family history:** None pertinent.

**Social history:** He is doing well in school.

**Physical examination:** Height 140 cm (5th percentile), weight is 62 kg (90th percentile). BMI third percentile. Pubertal examination is notable for 8 cc testicles and Tanner stage 2 pubic hair.





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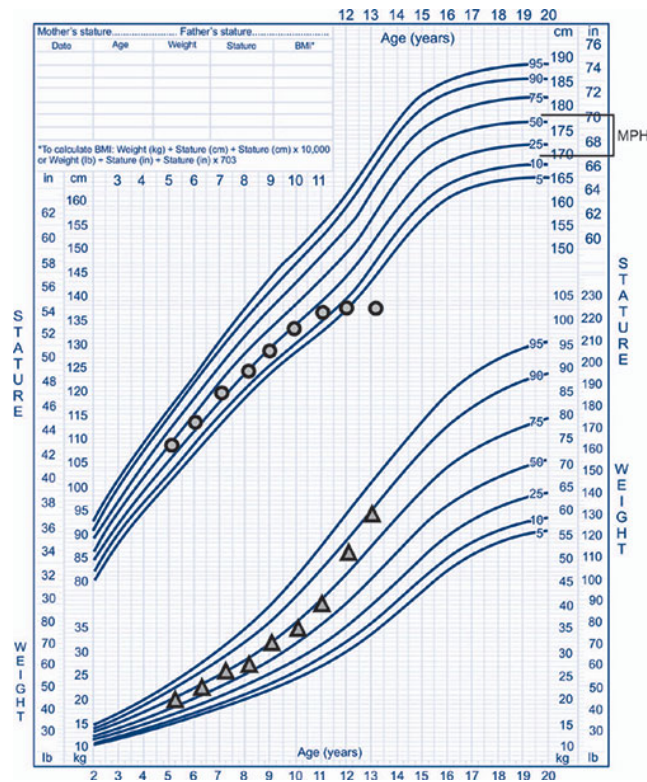


Figure 5: Growth chart (Case 4).

**Q: HOW DO YOU INTERPRET HIS GROWTH CHART?**

- Systemic disorders (GI, renal, pulmonary, cardiac, etc.) are associated with greater impairment of weight gain than linear growth
- Endocrine disorders are usually associated with relatively preserved weight gain or frank obesity in a short child
- His slowed height velocity with weight gain is concerning for an endocrine disorder.

**Q: IS HIS HISTORY OF ASTHMA LIKELY RELATED TO HIS SHORT STATURE?**

Yes, both excess endogenous and exogenous glucocorticosteroids are potent inhibitors of linear growth. The basal physiological requirement of glucocorticosteroids is 8–12 mg of hydrocortisone/m<sup>2</sup>/day. The equivalent glucocorticoid activity of other steroids is given in [Table 1](#).

Inhaled steroids can be especially potent since steroids absorbed via the pulmonary bed are not subject to first pass metabolism by the liver before entering the systemic circulation. Studies suggest that prolonged use of daily doses in excess of 500 µg of inhaled beclomethasone (or equivalent glucocorticoid activity of other synthetic steroids; fluticasone is 2–5 × more potent than beclomethasone) is associated with growth suppression. It should be discussed with him and his parents that the current dose of inhaled steroids (1,000 µg of fluticasone, which is equivalent to approximately 2,000–3,000 µg of beclomethasone) is significantly in excess of the 500 µg/day threshold of beclomethasone and hence it is likely that his growth delay is a consequence of the inhaled steroids. It is important to explain to the family that it is essential to prioritize his respiratory health and that changes in the dose of inhaled steroids must only be carried out as clinically tolerated and under the guidance of his pulmonologist.





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| <b><i>Steroid Potency</i></b>   |                     |      |
|---------------------------------|---------------------|------|
| <b><i>Equivalent Dosage</i></b> | <b><i>In Mg</i></b> |      |
| Cortisone                       | 25                  | 0.8× |
| Hydrocorticone                  | 20                  | 1×   |
| Prednisolone                    | 5                   | 4×   |
| Prednisone                      | 5                   | 4×   |
| Methylprednisolone              | 4                   | 5×   |
| Triamcinolone                   | 4                   | 5×   |
| Paramethasone                   | 2                   | 10×  |
| Betamethasone                   | 0.75                | 25×  |
| Dexamethasone                   | 0.5                 | 40×  |

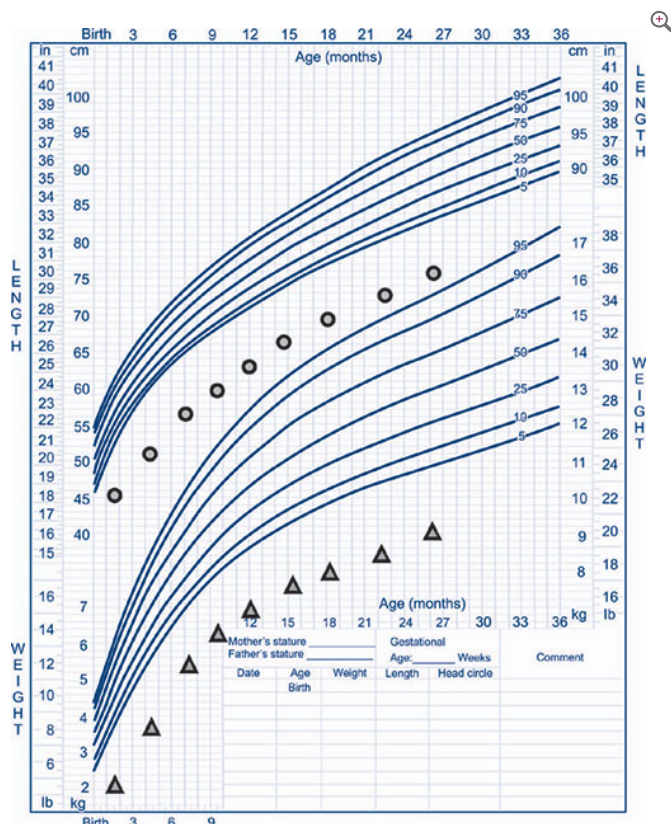
A 26-month-old toddler is referred for poor growth. He was born at 39 weeks gestation, weighing 1.6 kg. Perinatal history was unremarkable. Parents are unsure about history of neonatal hypoglycemia. He is a picky eater. Mother reports that he is being treated for chronic constipation. Growth chart is noted in [Figure 6](#).

**Past medical history:** None.

**Family history:** None.

**Development history:** He has delayed cognitive, language and social milestones.

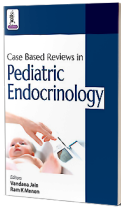
**Physical examination:** Height 77 cm (<3rd percentile), weight is 9 kg (<3rd percentile). He has a small, triangular face with prominent forehead, a narrow chin, a small jaw, and down-turned corners of the mouth. Clinodactyly is noted. He also has asymmetry in lower limb length.



**Figure 6:** Growth chart (Case 5).

### Q. WHAT IS THE DIFFERENTIAL DIAGNOSIS?

Small for gestational age (SGA) is most commonly defined as weight below the 10th percentile for the gestational age. At 39 weeks gestation the 10th percentile for weight is 2.50 kg (see [Table 2](#) with cut-off standards for SGA in Caucasian population). Hence this baby would be classified as SGA.



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There are many causes for SGA. In this baby, the constellation of SGA with phenotypic features of small triangular face with prominent forehead, narrow chin, small jaw, down-turned corners of the mouth, clinodactyly and limb asymmetry, and postnatal growth retardation is strongly suggestive of Russell-Silver syndrome (RSS). RSS is characterized by IUGR (birth weight >2 SD below mean) accompanied by significant (>2 SD below mean for weight and length) proportionate postnatal growth deficiency. Growth velocity is generally normal in children with RSS; the average adult height of males is 151 cm and that of females is 140 cm. These children are also at high risk for developmental delay (motor and cognitive) and learning disabilities.

**TABLE 2** Cut-off standards for small for gestational age (SGA) in Caucasian population

| <i>Gestational Age</i> | <i>Maximum Birth Weight (Gm)</i> | <i>Maximum Length (Cm)</i> |
|------------------------|----------------------------------|----------------------------|
| 26 weeks               | 703                              | 32.6                       |
| 27 weeks               | 746                              | 33.5                       |
| 28 weeks               | 813                              | 34.5                       |
| 29 weeks               | 898                              | 35.6                       |
| 30 weeks               | 1,023                            | 36.6                       |
| 31 weeks               | 1,140                            | 37.8                       |
| 32 weeks               | 1,277                            | 39.0                       |
| 33 weeks               | 1,400                            | 40.3                       |
| 34 weeks               | 1,553                            | 41.5                       |
| 35 weeks               | 1,717                            | 42.7                       |
| 36 weeks               | 1,889                            | 43.8                       |
| 37 weeks               | 2,118                            | 45.0                       |
| 38 weeks               | 2,333                            | 46.1                       |
| 39 weeks               | 2,500                            | 47.0                       |
| 40 weeks               | 2,560                            | 47.4                       |
| 41 weeks               | 2,617                            | 47.9                       |
| 42 weeks               | 2,553                            | 47.7                       |
| 43 weeks               | 2,446                            | 47.5                       |

**Q. IS THERE A CONFIRMATORY TEST FOR RUSSELL-SILVER SYNDROME?**

Russell-Silver syndrome is a genetically heterogeneous condition and the diagnosis is primarily based on identification of characteristic clinical features. A scoring system has been proposed with three major criteria or two major and two minor criteria qualifying for a diagnosis of RSS and justification to pursue confirmatory laboratory testing (Box 2).

Hypomethylation of the paternal imprinting center 1 of chromosome 11p15.5 is identified in 35–50% of individuals with RSS. About 10% of individuals with RSS have maternal uniparental disomy for chromosome 7.

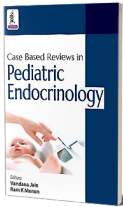
**Q. WHAT IS THE ROLE OF GH IN THE MANAGEMENT OF A CHILD BORN SGA?**

By definition, 10% of newborns are born SGA. Approximately 90% of term SGA infants display sufficient catch-up growth to attain a height above two SDs by the age of 2–3 years, whereas 10% remain short throughout childhood and adolescence. For the 10% of SGA children who lack catch-up, treatment with GH can increase linear growth. For SGA children with severe growth retardation, defined as height 2.5 or less SD score at age 2–4 years, early intervention with growth hormone should be considered at a dose of 35–70 µg/kg per day × 7 days a week.

The cause(s) for growth delay in RSS are not clear. GH deficiency has been described in RSS, although this is not a universal finding. Growth hormone therapy has been used to increase statural height in RSS in both patients with and without GH deficiency.

**Box 2 : Criteria For A Diagnosis Of Russell-Silver Syndrome**

- Major criteria
  - Intrauterine growth retardation/small for gestational age (<10th percentile)
  - Postnatal growth with height/length <3rd percentile



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- ◦ Normal head circumference (3rd-97th percentile)
- ◦ Limb, body, and/or facial asymmetry
- Minor criteria
  - ◦ Triangular facies
  - ◦ Frontal bossing/prominent forehead
  - ◦ Short (arm) span with normal upper- to lower-segment ratio
  - ◦ Fifth finger clinodactyly
- Supportive criteria
  - ◦ Hypoglycemia
  - ◦ Feeding disorder
  - ◦ Café au lait spots or skin pigmentary changes
  - ◦ Genitourinary anomalies (cryptorchidism, hypospadias)
  - ◦ Motor, speech, and/or cognitive delays

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## SUGGESTED READINGS

1. Chianese J. Short stature. *Pediatr Rev.* 2005; 26(1): 36–7.
2. Grimberg A, Lifshitz F, Bhargoo A, et al. Growth and growth disorders. In: Lifshitz F, editor. *Pediatric Endocrinology*, 5th ed. CRC Press; Florida: 2007. p. 1–188.
3. Rosenfeld R. Disorders of growth hormone and insulin-like growth factor secretion and action. In: Sperling MA, editor. *Pediatric Endocrinology*. 3rd ed. Elsevier Health Sciences; Philadelphia: 2008. p. 254–334.

